IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

UNITED STATES OF AMERICA, Plaintiff, v. BAYER CORPORATION Defendant.	Case No. 2:07-cv-00001 (Hon. Jose L. Linares) *Document Filed Electronically*

DEFENDANT'S OPPOSITION TO PLAINTIFF'S MOTION TO EXCLUDE THE TESTIMONY OF DR. ANDREW K. BENSON

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INTRODUCTION

The Court should deny the government's *Daubert* motion for three reasons.

First, the government has failed to address Dr. Benson's actual opinions: (1) geneticists and microbiologists do not require randomized, controlled, double-blind, product-specific, population-specific, human clinical trials; and (2) the species of bacteria in Phillips' Colon Health contain a shared genetic core that helps with the digestive symptoms at issue.

Second, the government applies the wrong standard for excluding testimony. Instead of challenging Dr. Benson's methodology as unreliable, *Daubert v. Merrell Dow Pharms, Inc.*, 509 U.S. 579, 589 (1993), the government challenges his conclusions for lack of "certainty."

Third, the government's criticism of Dr. Benson's testimony on short chain fatty acids is misdirected.

BACKGROUND

The government is seeking to hold Bayer in contempt on the basis of a novel and erroneous legal test. According to the government, Bayer must substantiate its probiotic supplement with Drug-Level Clinical Trials: "human clinical trials that (1) are randomized, placebo-controlled, and double-blind; (2) use the specific product for which the claims are made; (3) are performed in the population at which the claims are directed; and (4) use validated methods and appropriate statistical methods to assess 'outcomes.'" Dkt. No. 4-1 at 16. The government attempts to defend its novel

standard by contending that "experts in the field" require it. Dkt. No. 38 at 3; *see also* Dkt. No. 4-1 at 16. These experts include gastroenterologists, primary care physicians, geneticists, and microbiologists. Dkt. No. 73-1 Ex. G at No. 4-6 (government admissions).

In response, Bayer submitted four declarations from experts who explained that they and their colleagues do not require Drug-Level Clinical Trials for probiotic supplements. These experts were: a gastroenterologist (Dr. Brian Fennerty), a primary care physician (Dr. Daniel Merenstein), a geneticist and microbiologist (Dr. Andrew Benson), and a nutrition scientist (Dr. Jeffrey Blumberg). Dkt. No. 73-1 Ex. B-E. The first three also reviewed the substantiation for PCH and concluded that there is competent and reliable scientific evidence supporting Bayer's claims. *Id.*

The government sought to exclude *one* of Bayer's four experts, Dr. Benson,[1] who testified that geneticists and microbiologists do not require Drug-Level RCTs to support the probiotic claims at issue. Dkt. No. 73-1 Ex. D at 1-2 (hereinafter "Benson Dec."). He also testified that Bayer's claims are "valid and supported by competent and reliable scientific evidence." Benson Dec. at 16.

In offering this second opinion, Dr. Benson explained that it is appropriate to consider trials on other strains of the same species of bacteria because there is a

[1] Professor Andrew Benson is a geneticist and microbiologist who has studied the human gut microbiome for nearly two decades. He currently leads the University of Nebraska Gut Function Initiative, an internationally recognized, federally-funded research program in comparative and population genomics of bacterial species.

"shared core of genetic content" within the species. Benson Dec. at 6. This shared core "has been forged through evolutionary process" to drive "core metabolic functions of bacteria." *Id.* Among these core functions are regulating gut motility, influencing electrolyte transport, and degrading excess carbohydrates, which, in turn, help defend against constipation, diarrhea, gas and bloating. *See id.* at 8-15; *id.* at 6 ("gut microbiome does not generally behave in a strain-specific manner").

With respect to the genetic core, Dr. Benson indentified "shared metabolic pathways" that help produce short chain fatty acids ("SCFAs"). *Id.* 6-7, 11-12. These SCFAs "help with constipation diarrhea, gas and bloating," *see id.* at 7, and are among the many metabolic pathways common to all strains in the species. *See id.* at 18-21. One of the pathways (the "Bif Shunt Pathway") is "a defining characteristic of [the *Bifidobacterium*] genus." *Id* at 11.

Finally, Dr. Benson pointed to volumes of substantiation demonstrating the core benefits of the species of bacteria in PCH on gut physiology and health. *See id.* at 21-23. Within these volumes are "well-conducted meta-analyses" and "many randomized controlled trials on a variety of health end points." *Id.* at 21. Dr. Benson also noted that a similar conclusion was reached by an "expert panel that published the consensus scientific report in the prestigious journal *Nature Reviews Gastroenterology*," after examining "evidence gathered on a large number of different probiotic strains representing commonly studied species." *Id.* at 22 (citation omitted).

The government does not take issue with Dr. Benson's conclusion that geneticists and microbiologists do not require Drug-Level RCTs. Nor does the government address Dr. Benson's opinion—or his methodology in reaching the opinion—that each of the species of bacteria in Phillips' Colon Health contains a shared genetic core that helps with the digestive symptoms at issue.

Instead, the government's motion argues only that Dr. Benson has not established "with *certainty*" that SCFAs are a "clearly sufficient" mechanism, Dkt. No. 94-1 at 8, or that the SCFAs produced by PCH have the claimed effects, *id.* at 9. Because the government fails to address Dr. Benson's actual opinions, misapplies *Daubert*, and misunderstands Dr. Benson's testimony on SCFAs, the Court should deny the government's motion to exclude.

ARGUMENT

I. The Government Fails to Challenge Dr. Benson's Actual Expert Opinions.

The government does not address Dr. Benson's actual opinions. In his declaration, Dr. Benson first opined: "As a geneticist and microbiologist who has spent over 19 years studying population genomics of enteric bacterial species and the microbiome, I disagree with Dr. Laine's conclusion" that Drug-Level RCTs are required to substantiate probiotic claims. Benson Dec. at 1. Dr. Benson testified that geneticists and microbiologists do not require "the randomized controlled trials that Dr. Laine demands." *Id.* The government does not address this opinion.

The government also fails to address Dr. Benson's opinion that the shared core of genetic content in the three species of bacteria at issue "helps with digestive health including for constipation, diarrhea, gas and bloating." Benson Dec. 9. Dr. Benson explained that the "[s]hared core genes within a species have been shaped by evolutionary processes, and drive the basic functions of bacteria" including to help with digestive symptoms. Dkt. No. 114-1 Ex. C at 3 (hereinafter "Benson Supp. Dec."); *see id.* at 2 ("The ability of [the species] to provide general digestive benefits is evolutionarily-preserved across strains and genetically coded higher than the strain level."). "[I]t is clear that within the genetic content of these well-studied organisms exists the metabolic machinery to help with normal gut functioning." *Id.* at 9.

Dr. Benson's methodology of linking shared genetic content to core functions is well-established in the peer-reviewed scientific literature. *See* Benson Supp. Dec at 3 (citing numerous peer-reviewed articles supporting this methodology, referred to as "reverse ecology"). Dr. Benson himself has employed this methodology in numerous peer-reviewed publications. *See* Benson Supp. Dec. at 5 (citations 16-23). Even the government's expert, Dr. Bushman, agrees that Dr. Benson's methodology is established and accepted in the scientific community. Dkt. No. 81-2 at 9 (hereinafter "Bushman Dec.") ("[I]t is possible" to "infer aspects of [bacteria's] biological properties" from a "detailed comparison of genomes from different types of

bacteria."); *see also* Bushman Tr. 248:22-250:20[2] (responding that Dr. Benson's "methodology of predicting clinical outcomes based upon shared genes" is "definitely" something "that is done in the scientific community."); Bushman Tr. 276:10-12 ("The idea that shared gene content among organisms might correlate with shared properties of those organisms *is certainly a common idea.*") (emphasis added).

The motion ignores the detailed explanation of Dr. Benson's methodology, and even asserts that "Dr. Benson's report does not identify or explain what kind of scientific reasoning he uses, or what kind of scientific methodology he applies." Dkt. No. 94-1 at 11-12. The motion then mischaracterizes Dr. Benson's opinion by simplistically asserting that it is merely "based on two essential premises:" "(1) studies which purport to show that strains of *Bifidobacteria* and *Lactobacillus* bacteria other than those strains in PCH have some positive impacts on gastrointestinal function; and (2) all *Bifidobacteria* and *Lactobacillus* produce SCFA." Dkt. No. 94-1 at 1-2. The motion disregards the rest of Dr. Benson's methodology and analysis, which did not simply rest on these purported essential premises. Because the government's arguments are based upon a misstatement of Dr Benson's methodology and opinion, its *Daubert* motion should be denied.

[2] Dr. Bushman's deposition transcript has been filed with this Court, *see* Dkt. No. 114-1 Exhibit E.

II. The Government Applies The Wrong Legal Standard

In considering the reliability of an expert's testimony, the Court's inquiry must be based "solely on principles and methodology, not on the conclusions that they generate." *Daubert*, 509 U.S. at 595. Having nothing to criticize about Dr. Benson's methodology, the government asserts that this Court should exclude Dr. Benson's opinion because he "cannot say *with certainty* that SCFA[s] are a clearly sufficient mechanism of action," Dkt. No. 94-1 at 8 (emphasis added), or that the bacteria in PCH "impact the production of SCFA," *id.* at 9. But "certainty" is not the correct standard. In *Daubert* itself, the Supreme Court expressly rejected the requirement that "scientific testimony must be '*known' to a certainty*" as an *"unreasonable"* standard, *Daubert*, 509 U.S. at 590 (emphasis added). The Supreme Court explained that "certainty" *cannot* be required because "arguably, there are no certainties in science." *Id.* (citing amicus briefs from Nobel Laureate scientists and the American Association for the Advancement of Science).

The Supreme Court's admonition against requiring "certainty" is particularly appropriate in this case. This case is about a dietary supplement, not a drug. While a drug requires the "certainty" of two Drug-Level RCTs, 21 C.F.R. 5, § 314.126, a supplement does not, *see* 21 U.S.C. § 343(r)(6)(B). A supplement claim must merely be supported by "competent and reliable scientific evidence." FTC, *Dietary Supplements: An Advertising Guide for Industry* 3 (Apr. 2001), *available at* http://business.ftc.gov/documents/bus09-dietary-supplements-advertising-guide-

industry/ ("FTC Guidance"); *see also* Dkt. No. 2 at 2 (Bayer's consent decree requiring the same). FTC Guidance makes clear that under this standard, even animal and *in vitro* studies can be considered, *see id.* at 3, and it can be "appropriate to extrapolate from research to the claimed effect" even when there "are significant discrepancies between the research conditions and the real life use being promoted." *Id.* at 16. The law does not require certainty.

Nor do the relevant experts expect "certainty." As Dr. Benson explained, "certainty [is not] something [] geneticists and microbiologists expect, either in general or when studying probiotics in particular." Benson Supp. Dec. at 1; *see also id.* at 2 (noting that "scientists often do not have a comprehensive understanding of the mechanisms by which a drug or dietary supplement works"). If certainty were required, there would be little expert scientific testimony permitted in federal courts.

III. The Government's Discussion of Short Chain Fatty Acids Is Misguided.

In any event, the government's criticism of Dr. Benson's testimony on SCFAs is misguided. First, the government asserts that Dr. Benson does not know that "SCFA is the *only* mechanism of action." Dkt. No. 94-1 at 7 (emphasis added). This is true: Professor Benson acknowledged there "are very likely other mechanisms" beyond SCFAs "that remain to be discovered through which probiotics can help with constipation, diarrhea, gas and bloating." Benson Supp. Dec. at 2. But it is also irrelevant. As Dr. Benson explained, "scientists often do not have a comprehensive

understanding of the mechanisms by which a drug or dietary supplement works." Benson Dec. at 3.[3] Such an understanding is unnecessary to conclude that a product is effective. *Id.*; *see also* Fennerty Supp. Dec. at 5 ("[W]e do not need to know precisely how PCH works to know that it is effective"); Merenstein Supp Dec. at 3.

Second, the government contends that there are "significant gaps" in Dr. Benson's understanding of the SCFAs produced by the particular strains of bacteria in PCH. The government speculates, among other things, that the particular PCH strains might not produce enough SCFAs, might not survive, or might not persist long enough in the gut to have an impact. Dkt No 94-1 at 9-11. But the government offers no basis for this speculation.[4]

Nor does the government's geneticist. Indeed, Dr. Bushman recognizes that: (1) the production of SCFAs is "part of the shared core" of each of the species in PCH, Bushman Tr. 290:7-21; (2) "[t]he idea that shared gene content among organisms might correlate with shared properties of those organisms is certainly a

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[3] The government also erroneously asserts that Benson must "know[] [that] a change in the production of SCFA is a cause of diarrhea," Dkt. No. 94-1 at 6. This makes no sense—a mechanism need not be the *cause* of a symptom in order for that mechanism to help alleviate that symptom. For example, even though a lack of ibuprofen is not the *cause* of a headache, ibuprofen may help with the headache.

[4] Moreover, the government's geneticist stated that he did not even know if a probiotic had to survive or persist in order to have a beneficial impact. *See* Bushman Tr. 352:16-18 ("Do I know that probiotics must survive inside people in order to have a beneficial effect? No."); Bushman Tr. 350:8-13 (When asked whether "probiotics must persist in order to have a beneficial effect," Bushman explained "I don't have any opinion either way.").

common idea" "in the literature," *id.* 276:10-277-4; and (3) when you see the core genes, it can be "*probably pretty likely*" you will have the same clinical effect, "regardless of the strain," *id.* 263:13-19 (emphasis added); *id.* 271:6-272:5 ("reasonable chance" for EHEC E. Coli); *id.* 284:9-285:17 ("Commonly or frequently" the "Core genes define the species' specific characteristic"); *id.* 281:20-22 (agreeing that the core genome hypothesis has "dramatically influenced how bacteriologists think about bacterial species"). Although Dr. Bushman refused to apply this "common idea" to PCH in the absence of Drug-Level Clinical Studies, he offered no justification for doing so or for suggesting that PCH strains are deficient.[5] In any event, he admitted he is not an expert in any of these species, SCFAs, or probiotic interventions. Dkt. No. 122 at 3.

Further, the government again disregards much of Dr. Benson's testimony. Dr. Benson explained that the production of SCFAs by the three species at issue is "evolutionarily-preserved across strains and genetically encoded higher than the strain level." Benson Dec. at 2, 6. He also explained that the "gut microbiome does not

[5] In his report and at the deposition, he argued that "reversing the core genome hypothesis" makes sense here because he is aware of four disease (IBS) studies on other strains in these species that did not yield statistically significant positive results. Bushman Dec. at 21-22; *see also* Dkt. No. 94-1 at 2. But, even setting aside the fact that he is citing *disease* studies, his analysis is deeply flawed. He "incorrectly assumes that, if a species is effective, there could never be a null outcome (i.e., a p-value above .05). Benson Supp. Dec. 2-3. "Not only is this assumption mathematically and scientifically unsound, it ignores the fact that many effective products, including FDA-approved drugs, have studies with null results." *Id.*

generally behave in a strain-specific manner," *id.* at 6, and that the shared core "drives [the strains'] ability to impact normal gut functioning," and helps with "constipation, diarrhea, gas and bloating." *See* Benson Dec. at 6-7. Thus, he reasoned (by way of reverse ecology) that the PCH strains help defend against the digestive symptoms at issue. *See id.* at 7; Benson Supp. Dec. at 3.

Dr. Benson also drew support for this conclusion from the "many randomized controlled trials on a variety of digestive health end points," "several well-conducted meta-analyses," and the recent "consensus scientific report in the prestigious journal *Nature Reviews Gastroenterology*," *id.* at 21-23 (citing Colin Hill et al., *The International Scientific Association for Probiotics and Prebiotics Consensus Statement on the Scope and Appropriate Use of the Term Probiotic*, 11 Nature Reviews Gastroenterology & Hepatology 506, 508 (2014)). The government's assertion that Dr. Benson has "significant gaps in his understanding," Dkt. No. 94-1. at 9, is meritless. He might not have "certainty," but he has a methodologically sound and well-reasoned opinion, supported by volumes of evidence.

Finally, the government asserts that Dr. Benson's testimony ventures beyond his area of expertise. But, in the testimony the government cites, Dr. Benson merely stated that he had not personally "done [the] particular research on [the] signal transduction proteins [and] on those receptors" to show that that SCFAs help improve constipation, diarrhea, gas and bloating, because that "information is . . . in

the literature."[6] Dkt. 94-1 at 13 (citing Benson Tr. 197:6-14.). Dr. Benson did not have to personally repeat laboratory research in the public domain in order to testify about it. *United States v. Adams*, 189 Fed. Appx. 120, 123-24 (3d Cir. 2006) ("[I]t is perfectly acceptable for an expert witness to testify . . . to facts or data ascertained by persons other than the witness. Thus, the fact that the government's witness did not personally conduct the tests about which he testified is of no moment.").

CONCLUSION

The government's motion to exclude the Dr. Benson's testimony is meritless and should be denied.

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[6] Contrary to the government's assertion, Dr. Benson did not state that his "key assumption" is "that producing SCFA is clearly sufficient to explain the results observed in clinical research on other bacteria strains." Dkt. No. 94-1 at 12-13.

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